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Order and complexity in renal cell tumors. A cytogenetic, molecular genetic and histopathological study

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SUMMARY, CONCLUDING REMARKS, AND FUTURE PERSPECTIVES

Renal cell cancers (RCCs) are epithelial neoplasms that demonstrate a diversity of morphologic characteristics and clinical manifestations. Presently used classifications as from the WHO include gross, histological, and ultrastructural features, resulting in a classification of adenomas, renal cell carcinoma, and other tumors, without further subclassification. Based on such classifications, no conclusions can be drawn on oncogenesis, tumor progression and biological behavior (and subsequently differences in clinical behavior) of these tumors.

In 1986 a more extended and refined cytomorphologically defined subtyping of renal cell tumors, based on new electron microscopical and histochemical observations, was proposed by Thoenes and Störkel (1986). Based on the analysis of more than 1200 epithelial renal tumors, a relationship was suggested between cells of the different parts of the tubulus as cell of origin for different subtypes of renal cell carcinoma (Chapter 1). Chapter 2 deals with the cytogenetic as well as molecular genetic aspects of renal epithelial tumors. Cell suspensions from a large series of renal cell tumors were successfully cultured, and parts of tissue were fresh frozen (-80°C), parts embedded in paraffin for routine histology. Good quality karyotypes were obtained from about 90% of the cultures. The cytogenetic and molecular genetic studies indicate that certain specific chromosomal abnormalities correlate with different histological subtypes of renal tumors and their clinical behaviour, and may be important for the diagnosis and prognosis of these conditions. The clear cell and the chromophilic type are characterized by different specific chromosomal abnormalities: loss of heterozygosity on 3p is only found in the clear cell compact type and trisomy 17 in the (chromophilic) tubulo-papillary type. It appears that some of the chromosomal abnormalities occur alone or in specific combinations and show a correlation with tumor type or tumor grade. In the different subtypes of renal cell tumors, according to the classification as proposed by Thoenes *et al.* we found the chromosomal abnormalities shown in Chapter 2.1 and Figure 1. The most important are structural aberrations of chromosomes 1, 3, 4, 5q, 6, 10q, 11q, and 12q together with polysomy of chromosomes X, 4, 5, 7, 10, 12, 15, 16, 19, 20, 21, and 22, and monosomy of chromosomes 3, 8, 9, 13, 14, and loss of Y in the clear cell type. The main characteristics of the chromophilic type are trisomies 7 and 17, and loss of the Y-chromosome. Chromophobic carcinoma seems to be correlated with, among others, polysomy 7, trisomies 12, 16, 18, 19, structural abnormalities of 11q, and telomeric associations. Oncocytomas show trisomy 7. A subgroup of this tumors is characterized by t(5;11)(q35;q13) (Chapter 3.1). Trisomy 17 seems to be associated with tubulo-papillary growth pattern, because it was also observed in "mixed" tumors with clear cells and a tubulo-papillary growth pattern (unpublished observation). Monosomy 8, 9 and 14 seem to be correlated with a higher grade in clear cell tumors, as are polysomies 12, 16 and 20 in chromophilic tumors. Also structural aberrations (and probably loss of heterozygosity) of chromosomes 5q, 6, 10q, 11q, and 19 were found to be associated with tumor progression.

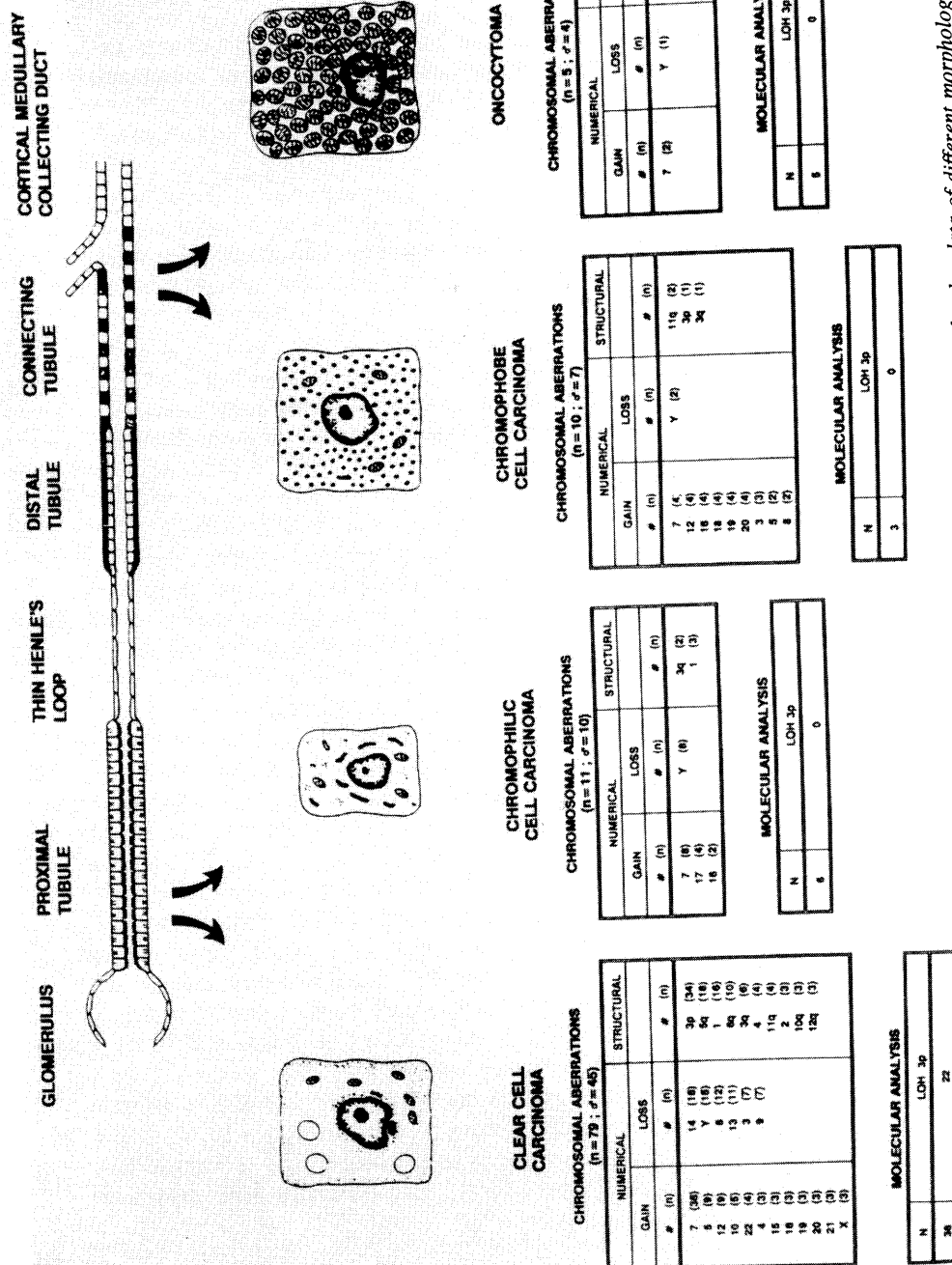


Figure 1 Most significant (present in > = 10% of the tumors) chromosomal abnormalities and molecular data of different morphological subtypes.

Abnormalities of the renal cell carcinoma (RCC) are involved. Most of the abnormalities are on chromosomes 3, 7, 12, 17, and 22. Whereas cytogenetic studies have revealed the same tumor trees. Analysis of presumed included in the frequency of Karyotyping misinterpretation of each other renal cell carcinoma. Thoenes and colleagues indicating tumorsuppression therefore To get more Y-chromosome tissue from these abnormalities clones with immune culture and Chapter one with cell tumor one of the two entities Chapter i(12p) is 80% of the with two coincident Adhesion tumors, focussed interact had a s extrac

Figure 1 Most significant (present in > = 10% of the tumors) chromosomal abnormalities and molecular data of different morphological subtypes.

	ccRCC	chRCC	oncocytoma
N	100	100	100
M	100	100	100

Abnormalities involving chromosomes 1, 16, 17, and 21 have also been found in other epithelial malignant lesions like carcinoma of the bladder, colorectum, breast and pancreas. In colorectal carcinoma chromosomes 1, 7, 8, 13, 17, and 18 seem frequently involved. Molecular genetic studies have pinpointed critical genes, e.g. *mcc* on 5q21, *p53* on chromosome 17, and *dcc* on chromosome 18, as important for tumorigenesis [1,2]. Whereas cytogenetic investigations are open-framed (all chromosome aberrations are revealed), molecular genetic analyses are highly specific (only those aberrations are revealed that one tests for) [3]. Heterogeneity and clonal evolution can be assessed by cytogenetics, but can cause a problem in molecular genetics [3]. We developed a new and objective method to visualize the relationships between different karyotypes from the same tumor in one patient through mapping cytogenetic changes on minimal spanning trees. Analysis of differences between karyotypes by using a minimum spanning tree as a presumed path of tumor evolution has two advantages: non-clonal abnormalities can be included in the analysis and differences found can be subjected to an objective form of frequency analysis.

Karyotyping on purely morphological grounds necessarily implies a significant risk of misinterpretation. The same is true for an analysis based solely on allelic losses by Southern blotting. Microscopic and molecular genetic techniques have to complement each other. Therefore, we analyzed loss of heterozygosity of chromosome 3 in matched renal cell tumor/normal kidney tissue pairs. Using the classification as proposed by Thoenes and Störkel (1986), allelic losses were restricted to the clear cell category, indicating that either only clear cell tumors arise as a consequence of loss of a tumorsuppressor gene on 3p, or in non-clear cell tumors the loss is more subtle and therefore undetectable, as yet (Chapter 2.2).

To get more insight in the role of certain frequent chromosomal abnormalities (loss of the Y-chromosome and trisomy 7 in particular) in oncogenesis, a large series of normal renal tissue from patients with RCC was studied (Chapter 2.3). These findings indicate that these aberrations might be involved in the process of (malignant) degeneration. Whether clones with trisomy 7 represent a subgroup of immunologic cells that participate in local immune reaction [in 4] or represent supposed epithelial-mesenchymal transition cells in culture as suggested by Herrmann *et al.* [4] remains to be elucidated.

Chapter 3 describes the discovery of a second subgroup of oncocytomas, apart from the one with -Y,-1, characterized by *t*(5;11)(q35;q13) (Chapter 3.1). In chapter 3.2 a clear cell tumor with oncocytic-like areas is described with the same breakpoint 11q13 as in one of the subgroups of the oncocytomas, possibly indicating a relationship between the two entities.

Chapter 4 deals with the finding of an *i*(12p) in a testicular metastasis of a RCC. An *i*(12p) is thought to be virtually specific for germ cell tumors where it is found in over 80% of cases. However, the possibility of a germ cell tumor was ruled out, which left us with two explanations: either this finding (as a secondary change) might be merely coincidental, or the host environment in the gonads favours tumor cells with an *i*(12p). Adhesion molecules are known to play an important role in the biological behavior of tumors, including tumor cell invasion and metastasis. The study described in Chapter 5 focussed on the expression of the molecules involved in cell-cell and cell-matrix interactions. In addition, we tried to determine whether different parts of the renal tubule had a specific micro-environment, as reflected by specific micro-environmental extracellular matrix protein composition in the different tumor subtypes. An attempt was

made to relate tumor-associated presence or absence of antigen expression to cytogenetic findings to see if tumorigenic changes cause disturbances function and/or antigen expression. No relationship could be shown. Our results show differential expression of the $\beta 1$ integrins, depending on histological subtype. No clear relationship with particular oncogenic changes of different parts of the tubular system was found. However, the number of cases is too limited and too unevenly distributed over the different subtypes to draw firm conclusions yet. It turned out that a distinction could be made between clear cell carcinoma and chromophilic carcinoma by differences in membrane expression of the vitronectin receptor (CD51) and VLA $\alpha 1$ (CDw49a) and by the presence of vitronectin in/on tumor cells. Oncocytomas were negative for VLA- $\alpha 5$ while the tumors from the proximal tubule were positive.

In chapter 6 cytogenetic results from two very rare, non-epithelial renal tumors are described: a carcinoid derived from neuro-ectodermal cells arising in the isthmus of a horseshoe kidney (Chapter 6.1) and a leiomyosarcoma of the kidney (Chapter 6.2).

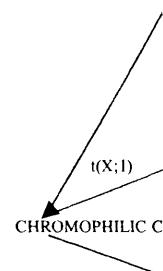
CONSEQUENCES FOR ONCOGENESIS OF RENAL CELL TUMORS

Different subtypes of renal cell carcinoma might originate from cells of the different parts of the renal tubulus. Taken together, cytogenetic and molecular genetic studies of recent years have demonstrated that certain specific chromosomal abnormalities correlate with different histological subtypes of renal tumors. Chromosomal abnormalities are believed to be responsible for neoplastic transformation, tumor growth and tumor progression [5]. Cancer genetic studies might reveal the cell of origin, oncogenic steps and relationship of tumors.

To date there are no really distinct criteria to reliably distinguish renal adenomas from carcinomas. About 99% of renal adenomas are chromophilic, no clear cell adenomas can be found. About 14% of the renal carcinomas are chromophilic and 75% are of the clear cell type, 3% of the renal carcinomas are mixed tumors of the clear cell and chromophilic type (other forms of mixture of basic tumor cell types have never been found).

So one might ask whether there is no relationship between renal cell adenomas and carcinomas, or whether there is progression from adenomas to chromophilic carcinomas to clear cell carcinomas. The chromosomal pattern of the different types of tumors, especially of the different parts of mixed tumors might reveal this relationship and progression model. A similar study was done in the adenoma-carcinoma sequence in colorectal neoplasia and revealed a series of consecutive genetic alterations involved [1]. The view of a relation between renal cell adenomas and carcinomas is strengthened by the fact that oncocytomas and adenomas occasionally show a malignant behavior. A reasonable explanation for this exceptional behavior is that oncocytomas and adenomas probably represent the benign side of a spectrum of renal cell tumors, with renal cell carcinoma at the other extreme. If the "spectrum" concept for adenomas and carcinomas is correct, then it may be expected that there would also exist an overlap in some of the characteristics of these benign and malignant tumors. Referring to this concept, the chromophobic carcinoma could be the malignant counterpart of the oncocytoma. Both show marker proteins and ultrastructural features of the distal nephron, thus disproving

the broadly accepted tubulus. At the (cytogenetic) level, see Figure 2.



Figure

FUTURE PER

It is well-known that it is too difficult to study the subtypes of renal cell carcinoma. The relationship between the different phenotypes is expanded to all subtypes, consisting of clear cell, chromophilic, and chromophobic. Studies of the role of differentiation and growth inducers like TGF- α and eosinophilic var-